REVIEW

Long-acting injectable antipsychotics (LAIs) for maintenance treatment of bipolar and schizoaffective disorders: A systematic review

Isabella Pacchiarotti\textsuperscript{a}, Jari Tiihonen\textsuperscript{b,c}, Georgios D. Kotzalidis\textsuperscript{d}, Norma Verdolini\textsuperscript{a,e,f}, Andrea Murru\textsuperscript{a}, José Manuel Goikolea\textsuperscript{a}, Marc Valentía\textsuperscript{a}, Alberto Aedo\textsuperscript{a,g}, Eduard Vieta\textsuperscript{a,*}

\textsuperscript{a}Barcelona Bipolar Disorders Program, Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, 170 Villarroel st., Barcelona, Catalunya, Spain
\textsuperscript{b}Department of Forensic Psychiatry, University of Eastern Finland, Niuvanniemi Hospital, Kuopio, Finland
\textsuperscript{c}Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
\textsuperscript{d}Neurosciences, Mental Health, and Sensory Organs (NESMOS) Department, Faculty of Medicine and Psychology, Sapienza University, Sant’Andrea Hospital, Rome, Italy
\textsuperscript{e}FIDMAG Germanes Hospitalàries Research Foundation, Sant Boi de Llobregat, Barcelona, Catalunya, Spain
\textsuperscript{f}Division of Psychiatry, Clinical Psychology and Rehabilitation, Department of Medicine, Santa Maria della Misericordia Hospital, University of Perugia, Perugia, Italy
\textsuperscript{g}Unidad de Trastorno Afectivo Bipolar, Departamento de Psiquiatría, Escuela de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

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Abstract
Long-Acting Injectable Antipsychotics (LAIs) are used to overcome non-compliance in psychoses, mainly schizophrenia spectrum disorders. We aimed to summarize available evidence of studies comparing the efficacy of LAIs to placebo or oral medications for Bipolar Disorder.
1. Introduction

Bipolar Disorder (BD) is a severe, recurrent and disabling mood disorder characterised by manic, hypomanic or mixed episodes, and alternating episodes of depression that affects approximately 2% of worldwide population (Grande et al., 2016). Affective episodes are recurrent and commonly associated with unfavorable outcomes, including poor cognitive performance and greater number of hospitalizations (Vieta et al., 2018). BD is typically associated with high mortality due mostly to cardiovascular diseases and an increased risk of suicide (Kendall et al., 2014; Kishi et al., 2016; Vieta et al., 2018). Moreover, BD is often associated with persistent symptoms leading to social and functional impairment (Martinez-Aran et al., 2009; Bortolato et al., 2015; Solé et al., 2018). Due to the chronic nature of the disorder and the negative consequences of unremitted or recurrent symptoms, BD requires long-term maintenance therapy to prevent future mood episodes as the primary goal of treatment after treating an acute affective episode. Despite lithium remains the gold standard prophylactic treatment for BD (Nivoli et al., 2010), patients may not accept lithium due to various reasons including monitoring requirement, side effects or poor adherence to treatment (Murrú et al., 2012, 2013). Thus, many patients require alternative prophylactic treatment for BD. Multiple studies and most BD treatment guidelines (Derry and Moore, 2007; Goodwin GM and Consensus Group of the British Association for Psychopharmacology, 2009; Grunze et al., 2013; National Collaborating Centre for Mental Health (UK), 2018; Yatham et al., 2018) recommend the use of oral second-generation antipsychotics (SGAs) as a long-term option for BD and many SGAs have official European Medical Agency (EMA) approval for this indication.

Similarly, schizoaffective disorder (SAD) is a chronic and severe illness consisting on the concurrent presentation of symptoms of schizophrenia and affective disorders (depression and/or mania) (Murrú et al., 2016). Actually, there is a still unresolved debate on nosological distinctions among schizoaffective disorder (SAD), BD-I with psychotic features and schizophrenia (SZ) (Tondo et al., 2016).

Adherence to medication is essential for BD and SAD patients to respond satisfactorily to treatment. Nonetheless, the frequency of nonadherence in BD and SAD patients bipolar type is estimated to range between 10% and 60% (9,10,18) even during euthymic periods (Colom et al., 2000). Nonadherence increases the risk of relapse and suicide (Samalin et al., 2014) as well as the risk of rehospitalization (Gigante et al., 2012). It should be stressed that despite patients’ will to receive LAI treatment, this type of treatment is still less used in patients discharged after hospitalization for a psychotic episode (Hamann et al., 2014), even if their long-term safety has been demonstrated (Lindenmayer et al., 2007).

Long-acting injectable (LAIs) antipsychotics, including first-generation depot antipsychotics (FGDAs) and second-generation depot antipsychotics (SGDAs) may improve treatment adherence in patients with psychiatric illness requiring long-term maintenance treatment (Gigante et al., 2012; Llorca et al., 2013). LAIs have been shown to decrease the rate of relapse and hospitalization in patients with schizophrenia (Correll et al., 2016). The use of LAIs in the maintenance treatment of BD and SAD has raised interest for improving adherence and reducing the risk of relapse (Gigante et al., 2012; Samalin et al., 2014; Kishi et al., 2016). In a recent, large population-based observational cohort effectiveness study (N = 18,018) based on the Finnish registry of the whole population of Finland (Lahteenvuo et al., 2018), the most effective treatments to prevent re-hospitalization in BD patients were lithium and LAIs, with 30% of rehospitalization risk reduction with LAIs compared to the same medications in oral formulations. To date, FDA has approved the use of risperidone-LAI (RIS-LAI) as both monotherapy and as adjunct therapy to lithium and valproate for the maintenance treatment of BD-I. Recently, FDA has approved aripiprazole monohydrate extended-release injectable suspension (Ari-M) for the maintenance monotherapy treatment of BD-I. RIS-LAI
and recently paliperidone palmitate (Pal-P) have received EMA indication for SAD disorder. On the contrary, no LAI has current EMA indication for BD. Although FGDAs have been studied in BD, they have not been approved for use in this disorder (Gigante et al., 2012).

To summarize the available evidence, we conducted a systematic review of studies comparing the efficacy and safety of first- and second-generation depot antipsychotics (FGDAs and SGDAs, respectively) to placebo (PBO) or oral medications for BD and SAD. We decided to include in this review also SAD due to the similarities in acute and long-term need for treatments aimed at manic, mixed, depressive, or psychotic conditions, both psychotic and nonpsychotic, that justify a conceptual framework of continuity across these two conditions (Murru et al., 2016; Argolo et al., 2018).

2. Procedures

This review has been conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher et al., 2009). Search Methods and Results are highlighted in Fig. 1.

2.1. Literature search

We systematically searched the MEDLINE/Pubmed/Index Medicus, Cochrane Library, CINHAL, PsycINFO/PsycARTICLES, clinicaltrials.gov, and Scopus databases from any time to 28 March 2018, cross-checking the obtained references. The systematic search was performed by two blind independent research teams (led by IP and GDK), searching as follows:

- MEDLINE/PubMed/Index Medicus: authors used the following search strategy: (depot OR once-monthly OR 3-month OR long-acting OR LAI[ti] OR LAI[ti] OR monohydrate OR haloperidol OR palmitate OR pamoate OR microsphere OR dodecanoate OR decanoate OR enanthate OR oenanthate OR acetate OR consta OR maintena OR zypadhera OR xeplon OR sustenna OR trinza) AND (aripiprazole OR olanzapine OR risperidone OR paliperidone OR risperdal OR 9-OH-risperidone OR 9-hydroxyrisperidone OR haloperidol OR fluphenazine OR flumantixol OR flupenthixol OR zuclopenthixol OR pipothiazine) AND (bipolar disorder OR bipolar depression OR mania OR manic OR schizoaffective) that produced 374 records. Of them, duplicates were 0, and selected for analysis 13.
- For the Cochrane Library we used the same search strategy, save for the use of square brackets, that the database’s system does not accept; the search produced 144 records, one of which unlocalisable. It added no inculdable record to the PubMed search.
- With the other databases we performed the same search as for PubMed. CINHAL yielded 92 records.
- PsycINFO/PsycARTICLES yielded 365 records.
- Scopus produced 37 records.
- For the https://clinicaltrials.gov/ database, keywords were: long-acting antipsychotics AND bipolar disorder OR schizoaffective disorder and produced 29 records. Of all databases used and the additional 15 records that were identified through other sources/reference lists, none added an includible article to the pool of records identified by and selected from PubMed.

2.2. Study selection

We included longitudinal studies of the effect of LAIs in the treatment of patients with BD and SAD. Studies could be experimental (randomized clinical trials (RCT), quasi-RCTs, nonRCTs), quasi-experimental (controlled before and after studies, interrupted time series), and observational (cohort, case-control, registry studies). We excluded animal studies, and studies resulting from databases but not being relevant as to the effects of the administration of LAI antipsychotics in patients with BD or SAD. Excluded were also studies on the effects of LAIs on mixed schizophrenia/schizoaffective disorder patients without reporting results separately. Meta-analyses and reviews were used as evidence to support information that could not be drawn from individual studies. Open studies, unless they had a mirror design with a retrospective period equal to the longitudinal prospective one, case reports or series, pharmacoeconomy studies not providing clinical outcomes, letters to the editor, author responses to criticisms, opinion papers, editorials, studies focusing only on biomarkers, like genetic investigations and brain imaging, pharmacokinetic studies, technical studies focusing on types of formulations or study designs, were excluded. Congress Abstracts, despite not being subjected to peer reviewing, were considered if they provided sufficient data for analysis and they were not subsequently published in regular papers.

For this review, we filled-in the PICO worksheet (Miller, 2001), the AMSTAR form (Shea et al., 2017), and the PRISMA checklist (Moher et al., 2009), which we provide as an online Supplementary file. We assessed the quality of included trials with Jadad’s et al. (1996) scale for the evaluation of randomized control trials and the strength of our recommendations with the National Health and Medical Research Council (NHMRC) of the Australian Government’s (2009) NHMRC levels of evidence and grades for recommendations for developers of guidelines. Risk of bias was addressed with taking into account the Cochrane Risk of Bias Tool (Higgins and Green, 2011), classifying every study according to a high, low, unclear category for the selection, reporting, performance, detection, attrition, and other dimensions, which then affected the global quality of the paper.

3. Results

3.1. Systematic search results

The pooled records amounted to 640 Records (Fig. 1). Excluded were: 114 Reviews, 113 NBSA, 77 No LAI, 65 Open (open design-no mirror), 130 Case (reports/series), 0 Inadeq (inadequate design or outcomes), 33 E/O (editorials/opinion papers), 13 PhE (Pharmacoeconomic studies), 14 Surveys, 1 Biotech (biotechnologies, laboratory), 15 PhK (pharmacokinetics), 12BM/Gen (biomarkers, brain imaging,

Records identified through database searching (n = 1041)

Additional records identified through other sources (n = 13)

Records after duplicates removed (n = 642)

Records screened (n = 642)

Full-text articles assessed for eligibility (n = 642; one not localizable)

Studies included in qualitative synthesis (n = 15)

- Double-blind: 6 (5 bipolar, 1 schizoaffective)
- Open-label: 9 (8 bipolar, 1 schizoaffective)
- Per LAI drug: risperidone 11, flupenthixol 2, aripiprazole 1, paliperidone 1
- Per disorder: bipolar 13, schizoaffective 2

Full-text articles excluded, with reasons (n = 626)

- 114 Reviews
- 113 No BD, no schizoaffective
- 77 No LAI
- 67 Open/sad design
- 130 Case (reports/series)
- 0 inadequate reporting
- 33 editorials/opinion/letters
- 13 pharmacoeconomy
- 14 Surveys
- 1 Biotechnology
- 15 pharmacokinetics
- 12 biomarkers/genetics/neuroimaging
- 3 Technical
- 3 Animal/Cell cultures
- 30 Same data as others
- 1 secondary analysis of other

Fig. 1 PRISMA flow diagram and results of our literature search, including reasons for exclusion and typology of included studies. From Moher et al. (2009) www.prisma-statement.org.

or genetics), 3 Technical, 3 Animal/Cell (studies on nonhumans or on isolated cell tissues), 1 was a secondary analysis of the data of another study that had changed the primary outcome to a part of the primary outcome of the other (i.e., time to hospitalization instead of time to recurrence, which was defined in part also by hospitalization) and 30 Same (reporting data elsewhere published better). 1 was not possible to localize. This left 15 records to include (Fig. 1). We included 6 double-blind studies and 9 open studies. 13 studies assessed BD and 2 SAD. One trial tested aripiprazole monohydrate once monthly (double-blind, BD); 2 trials assessed the use of flupenthixol depot (1 double-blind, 1 open, BD); 1 trial tested paliperidone palmitate (double-blind, SAD); 11 trials assessed RIS-LAI (8 open-3 double-blind, 10 BD-1 SAD). The details of each study are reported in Table 1.

Most studies were of good to satisfactory quality of evidence, but none was excellent, despite some studies had included large samples (Table 1). Reasons varied, with all multisite studies not addressing intersite variability issues, high rate of attrition bias, not clearly disclosed method of randomization, small samples, and possible sponsor bias. Hence, the total strength of recommendations of this review according to the National Health and Medical Research Council (NHMRC) (2009) is from satisfactory to good.

3.2. Content results

3.2.1. First-generation depot antipsychotics (FGDA)

Two studies have been included regarding the use of flupenthixol depot in BD patients as alternative to lithium. The first (Ahlfors et al., 1981) was a non-blind, randomized study with flupenthixol decanoate vs. lithium in 33 BD patients who had experienced at least three manic or depressive episodes during the last 5 years before the enrolment. The results showed no differences in terms of number of episodes per year and in time spent ill between the two groups. Also comparing the 5 years pre-trial, neither flupenthixol nor lithium showed significant prophylactic effect against mood episodes. In the second RCT study (Esparn et al., 1986), 15 patients were randomized to flupenthixol 20 mg/month or PBO as adjunctive treatment to lithium.
Table 1  Summary of included studies in reverse chronological order, their quality/risk of bias assessment, and their typology.

<table>
<thead>
<tr>
<th>Studies by first author and date in reverse order</th>
<th>Study design</th>
<th>Population, n (sites; sp. Y/N)</th>
<th>Duration</th>
<th>Drug</th>
<th>Main outcomes</th>
<th>Quality (includes bias)</th>
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<tr>
<td>Hsieh et al. (2017)</td>
<td>Open RIS-LAI mirror (BD, rapid and non-rapid cycling stratification was performed)</td>
<td>287, 251 noncycling, 36 rapid cycling (National database; N)</td>
<td>12 months</td>
<td>RIS-LAI (mean dose: 24.6 mg/2weeks) as add-on to TAU during 1 year (n = 287)</td>
<td>- The prevalence of concomitant use of TAU decreased from the pre-RIS-LAI period to the post-RIS-LAI period</td>
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<td>Calabrese et al. (2017)</td>
<td>DB Ari-M vs. PBO withdrawal surv (BD-I)</td>
<td>266 (103, 7 countries in 3 continents; Y)</td>
<td>52 weeks</td>
<td>Ari-M (400 mg/1 month) (n = 133 completers = 64) vs. PBO (n = 133, completers=38)</td>
<td>- Time to recurrence of any mood episode: Ari &gt; PBO</td>
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<td>Chan et al. (2016)</td>
<td>Open RIS-LAI mirror (BD-I) pre- and post-1 year RIS-LAI</td>
<td>469 (1; N)</td>
<td>12 months</td>
<td>RIS-LAI + TAU (2 groups, compliant and non-compliant n = 77) vs. SGA + TAU (2 groups NRIS-LAI, compliant and non-compliant n = 392)</td>
<td>- Re-hospitalization rates were significantly lower in the post RIS-LAI1 group than pre-RIS-LAI1 period for any mood episode, manic and depressive episodes</td>
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<td>Fu et al. (2015)</td>
<td>DB Pal-P vs. PBO surv (SAD)</td>
<td>334 (84, 8 countries in 4 continents; Y)</td>
<td>15 months</td>
<td>Pal-P once monthly + TAU or monotherapy (SAD n = 164) vs. PBO + TAU (SAD n = 170)</td>
<td>- Rates of emergency room visit were significantly lower in the RIS-LAI1, RIS-LAI2 and NRIS-LAI1 groups compared with those before enrollment</td>
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<td>Vieta et al. (2012)</td>
<td>DB RIS-LAI vs. PBO surv (BD-I)</td>
<td>398 (34 in 4 continents; Y)</td>
<td>18 months</td>
<td>RIS-LAI (22, 37.5 or 50 mg/2 weeks, n = 132) vs. PBO (n = 135) vs. third arm Olaprazole (10 mg/d) (n = 131)</td>
<td>- Time to relapse for psychotic, depressive, and manic symptoms: Pal-P in add-on or monotherapy &gt; PBO</td>
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<tr>
<td>Bobo et al. (2011)</td>
<td>Open, randomized RIS-LAI (BD-I and II rapid cycling)</td>
<td>50 (1; Y)</td>
<td>12 months</td>
<td>RIS-LAI + TAU (n = 25) vs. TAU (n = 25)</td>
<td>Rates of any-cause relapse events: RIS-LAI + TAU = TAU Duration of relapse events (any cause): RIS-LAI + TAU = TAU Number of negative clinical events: RIS-LAI+TAU &lt; SGA+TAU</td>
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<td>Chengappa et al. (2010)</td>
<td>Open, randomized RIS-LAI vs. oral (BD-I and II)</td>
<td>48 (3; Y)</td>
<td>15 months</td>
<td>RIS-LAI (25, 37.5 or 50 mg/2 weeks) + TAU (n = 25) vs. SGA (Ari, Ola, Que Zip) + TAU (n = 25)</td>
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<td>Quiroz et al. (2010)</td>
<td>DB RIS-LAI vs. PBO, surv (BD-I)</td>
<td>303 (57, 10 countries in 3 continents; Y)</td>
<td>24 months</td>
<td>RIS-LAI (12.5, 25, 37.5 or 50 mg/2 weeks) (n = 154) vs. PBO (n = 149)</td>
<td>Time to recurrence: RIS-LAI−PBO (significant differences for elevated mood episodes but no for depressive episodes) Compared to the pre-RLAI initiation period, at 12 months post-initiation completers had greater reductions than discontinuers in the percent of patients hospitalized and in the length and number of hospital stays, differences that remained at 24 months.</td>
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<td>Peuskens et al. (2010)</td>
<td>Open RIS-LAI discont. SAD vs. schizophrenia</td>
<td>1659 (6 nationwide databases in 2 continents; Y)</td>
<td>24 months</td>
<td>RIS-LAI completers after 2-years (mean dose: 42.3 mg/2weeks) (SDA n = 171) vs RIS-LAI discontinuers after 2 years (mean dose: 48.8 mg/2 weeks) (SDA n = 32)</td>
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<td>Macfadden et al. (2009)</td>
<td>DB add-on RIS-LAI (BD-I and II)</td>
<td>124 (32, 2 countries from 2 continents; Y)</td>
<td>12 months</td>
<td>RIS-LAI (25, 37.5 or 50 mg/2 weeks) + TAU (n = 65) vs PBO + TAU (n = 59)</td>
<td>Time to recurrence: RIS-LAI + TAU &gt; PBO + TAU</td>
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<tr>
<td>Vieta et al. (2008)</td>
<td>Open mirror RIS-LAI (BD-I)</td>
<td>29 (1; N)</td>
<td>24 months</td>
<td>RIS-LAI + TAU(n=29) (mean starting dose = 34.4 mg, mean final dose = 46.4 mg)</td>
<td>- Decreased number of hospitalizations (not due to depression) - Decreased average length of hospitalizations per patient - Increased time to any relapse - Improvement in treatment adherence</td>
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<td>Yatham et al. (2007)</td>
<td>Open, randomized RIS-LAI (BD I and II)</td>
<td>49 (8 in 1 country; Y)</td>
<td>6 months</td>
<td>RIS-LAI (25 mg/2weeks) + TAU (n = 23) vs. SGA (Ola, Que, Ris) + TAU (n = 26)</td>
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differences were found between flupenthixol and PBO in the average number of days hospitalized during the depot period. When total scores were calculated on the Affective Morbidity Index, ratings for depression were worse for the flupenthixol group, although this result was not statistically significant.

### 3.2.2. Second-generation depot antipsychotics (SGDA)

We identified eleven clinical studies that investigated RIS-LAI in BD or SAD patients, 1 investigating Pal-P and 1 Ari-M. These included 8 open label prospective or mirror studies and 5 RCT. 

**Open-Label studies and unblinded controlled trials.** Savas et al. (2006) examined the charts of 12 BD I predominantly manic patients, with no substance abuse and nonadherent to oral medication who received RIS-LAI 25-50 mg/2 weeks started during a manic or hypomanic state during 6 months either in monotherapy or in combination with a mood stabilizer. No manic or depressive episodes were observed during depot treatment. A significant reduction in Clinical Global Impression Scale (CGI) was found, while there were no changes in Hamilton Depression Rating Scale (HAM-D) scores.

An open, randomized active comparator trial with RIS-LAI vs. oral atypical antipsychotic agents (AAP) was reported by Yatham et al. (2007) in BD I or II patients currently on one oral SGA who had Young Mania Rating Scale (YMRS) and Montgomery-Asberg Depression Rating Scale (MADRS) between 13 and 19 and CGI scores between 3 and 4 (mildly to moderately ill). Patients were randomized to receive RIS-LAI 25-50 mg/2 weeks or to continue previous oral SGA during 6 months. Mood stabilizers and antidepressants were permitted. Patients on RIS-LAI but not those on oral SGA improved significantly in CGI-S and YMRS scores at 6-month follow-up. In contrast the oral SGA group had significant reductions in Hamilton Anxiety Rating Scale (HAM-A) scores relative to baseline compared to BD patient treated with RIS-LAI.

Vieta et al. (2008) assessed 29 acutely manic BD I patients who had one or more previous hospitalisations for mania and with a history of non-adherence to medication in a naturalistic two-year follow-up study. Patients received 25-50 mg/2 weeks of RIS-LAI plus a mood stabilizer and other commonly prescribed medication but no other oral antipsychotics were allowed. Outcomes were compared with a previous period of one year before initiating RIS-LAI. The authors found a significant reduction in treatment discontinuation, a decrease in the number of hospitalizations per patients, a significant decrease in hospitalisations for mania or mixed episodes with RIS-LAI. No significant decreases in hospitalization rates for depression were found. Moreover, the mean length of stay per patient significantly decreased and time to relapse to any mood episode increased. Finally, improved CGI scores and decreased aggression were found with RIS-LAI.
Peuskens et al. (2010) assessed treatment retention (vs. discontinuation) on RIS-LAI and outcomes in schizophrenia and SAD patients for whom 24 months of follow-up data in the electronic Schizophrenia Treatment Adherence Registry (e-STAR) were available.

Data were available for 171 RIS-LAI completers vs. 32 RIS-LAI discontinuer SAD patients. Compared to the pre-RLI initiation period, at 12 months post-initiation completers had greater reductions than discontinuers in the percent of patients hospitalised (66.2% reduction vs. 29.2%) and in the length (68% reduction vs. 0%) and number (80.0 vs. 14.3%) of hospital stays, differences that remained unaltered after 24 months.

In a randomised, but open-label, 15-month pilot trial assessing clinical effectiveness, Chengappa et al. (2010) assessed the efficacy of RIS-LAI compared to oral SGAs in BD-I or -II during a manic, hypomanic or mixed episode. The study provided for a 3-month titration and stabilization phase followed by a 1-year extension phase. The results of the study showed that RILAI-treated patients experienced significantly fewer negative clinical events (47 negative clinical events were recorded in terms of outcome and other safety measures) than AAP-treated patients.

Bobo et al. (2011) compared adjunctive RIS-LAI plus treatment as usual (RLLA1+TAU) in a 12-month randomised open comparison of RLLA1+TAU (N = 20) and TAU alone (N = 25) in BD-I or -II with rapid cycling course. The results showed no significant between-groups differences in the total number or duration of relapse events (any cause) or in the number of manic or depressive relapses. RIS-LAI treatment significantly reduced the need for urgent care referrals or the frequency of medication adjustments to prevent relapses.

In a retrospective cohort study, Chan et al. (2016) assessed the effect of RIS-LAI treatment on BD-I patients treated with RIS-LAI and different oral SGAs and followed during 1 year. On the basis of RIS-LAI use and treatment compliance, BD-I patients were classified into 4 groups: compliant patients receiving RIS-LAI treatment (LAI1), noncompliant patients receiving RIS-LAI treatment (LAI2), compliant patients receiving oral medications (NALI1), and noncompliant patients receiving oral medication (NALI2). After 1-year of follow-up, re-hospitalization rates were significantly lower in the LAI1 group than that before enrolment for any episode (manic episodes (p = 0.005); depressive episodes (p = 0.002). Emergency room visit rates were significantly lower in the LAI1 (p = 0.0001), LAI2 (p = 0.013), and NLAI1 (p = 0.0001) groups, compared to the respective pre-enrolment rates.

Recently, a 1-year mirror-image naturalistic study using a national claims database (Hsieh et al., 2017) assessed RIS-LAI treatment in BD-I patients. Rapid and non-rapid cycling stratification was performed based on the number of change-in-mood episodes within 1 year prior to the index date. The authors found that the prevalence of concomitantly used of TAU decreased from the pre-RIS-LAI period to the post-RIS-LAI period. RIS-LAI use decreased emergency room (ER) visits, hospital admissions, length of hospital stay, and non-medication costs. Moreover, RIS-LAI use decreased the number of change-in-mood episodes in rapid cycling patients.

Double-blind, randomised PBO-controlled trials. MacFadden et al. (2009) reported the results of a double-blind randomised, PBO-controlled trial with RIS-LAI 25-50 mg/2week as adjunctive treatment to TAU in frequently relapsing BD-I patients (who had experienced 4 or more episodes during the past year). Patients were stabilized in a 16-week open-label phase with RIS-LAI and then randomised to continue RIS-LAI (n = 65) or switch to PBO (n = 59). Both groups continued with TAU, which included mood stabilizers and other medications, but not oral antipsychotics. The results showed that the relative risk of relapse was 2.3-fold higher with PBO compared with RIS-LAI group. A significant delay in time to recurrence to any mood episode was observed with RIS-LAI. Moreover, a significant increase in YMRS scores and CGI-BP-S mania and overall scores was found in the RIS-LAI group compared with PBO, while no differences were found in MADRS scores and CGI-BP-S depression between the two groups.

A 24-month randomised, double-blind, PBO-controlled study with RIS-LAI in monotherapy was conducted by Quriroz et al. (2010) on acute manic/mixed (YMRS ≥ 20) or stable (CGI-S score ≤ 3) BD-I patients, but requiring change of medication to depot due to safety or tolerability concerns. Patients were excluded from the study if they had more than 4 episodes/year in the 2 years before the screening (rapid cycling). BD-I patients started on the 26-week open-label stabilization phase with RIS-LAI. During the randomisation phase, 154 patients received RIS-LAI 25-50 mg/2 weeks and 149 PBO, with a follow-up of 24 months. Results showed a significant delay in time to relapse in the RIS-LAI group compared to PBO for any mood episode (p < 0.001) and lower rates of recurrence with RIS-LAI (30% with RIS-LAI vs. 56% with PBO). RIS-LAI significantly prolonged time to discontinuation for any reason compared to PBO. Nonetheless, time to recurrence was longer for RIS-LAI group compared with PBO group only for manic/hypomanic episodes but not for depressive episodes. RIS-LAI was significantly superior in maintaining the YMRS, MADRS, and CGI-S scores than PBO.

Later, the efficacy of RIS-LAI for preventing recurrence of mood episodes in BD-I patients was evaluated in another randomised, PBO-controlled study (Vieta et al., 2012). After a 12-week open-label stabilization period with RIS-LAI (N = 560), patients who did not experience a recurrence entered an 18-month randomised, double-blind period with RIS-LAI (N = 132), PBO (N = 135) or with olanzapine 10 mg/day (N = 131) as third treatment arm for reference and exploratory comparisons. Time to recurrence of any mood episode was significantly longer with RIS-LAI vs. PBO (log-rank test stratified by region only, p = 0.031). Similarly to previous studies, differences were significant for time to recurrence of manic/hypomanic episodes (p = 0.005) but not depressive episodes (p = 0.695).

Regarding the efficacy of paliperidone palmitate (Pal-P) the only study included is a double-blind, PBO-controlled trial on SAD patients (Fu et al., 2015). SAD patients experiencing acute psychotic and depressive/manic symptoms were stabilized with Pal-P monthly as monotherapy or as adjunctive therapy to mood stabilizers or antidepressants. After an open-label stabilization period of a 13-week, flexible-dose and of a 12-week fixed-dose, patients and randomly assigned to Pal-P monthly (N = 164) or PBO (N = 170)
in a 15-month, double-blind, relapse-prevention phase. Pal-P significantly delayed time to recurrence for psychotic, depressive, and manic symptoms compared with PBO (p < 0.001, log-rank test). Relapse risk was 2.49 times greater for PBO (hazard ratio = 2.49; 95% CI, 1.55 to 3.99; p < 0.001). Moreover, Pal-P was superior to PBO in maintaining functioning as measured by the Personal and Social Performance scale (p = 0.014, mixed-model repeated-measures analysis).

Recently, Calabrese et al. (2017) reported the results of a 52-weeks, randomized, double-blind, PBO-controlled trial on the efficacy of aripiprazole monohydrate depot (Ari-M) 400 mg once-monthly as maintenance treatment of BD-I. BD-I patients experiencing a manic episode were stabilized sequentially on oral aripiprazole and Ari-M 400 mg (18-26 weeks) and then were randomised to Ari-M 400 mg (N = 133) or PBO (N = 133) during a 52-week follow-up period. 64 patients on Ari-M and 38 patients on PBO completed the study. Ari-M 400 significantly delayed time to recurrence of any mood episode compared with PBO (p < 0.0001). Significantly fewer patients (p < 0.0001) experienced recurrence of any mood episode with Ari-M 400 (35/132; 26.5%) compared with PBO (68/133; 51.1%), with stronger effects on manic episodes (p < 0.0001).

4. Discussion

We here performed a systematic review of the efficacy of LAI treatments in BD and SA; we rated our review according to the AMSTAR system and we found it to be of moderate quality (Shea et al., 2017). The present systematic review examined the efficacy of LAIs for maintenance treatment of BD and SA compared with PBO and oral medications. Regarding FGDAs, although there are not head-to-head comparisons between FGDAs and SGDAs, the trials reviewed indicate that there are some differences between these two AP groups. Depot Flup-D was the AP most investigated. There are only two controlled studies and they are negative. The PBO controlled study with Flup-D added to lithium and the comparison of Flup-D vs. lithium did not show differences in days of hospitalization, number of episodes/year and time spent ill (Ahlfors et al., 1981; Esparon et al., 1986). Moreover, the negative results of Esparon’s et al. randomized trial (1986) might be due to the lack of effect on depression or a possible worsening of depression with Flup-D compared to PBO, even if the more severe depression found in six of eight Flup-D-treated patients was not statistically significant. Overall, FGDAs might be as effective as lithium in preventing manic episodes, but without efficacy on depressive recurrences, and they might even worsen depressive symptoms. Limitations of FGDAs studies include the lack of adequate sample sizes, comparators arms and outcome measures for mood disorders. Furthermore, their time-frame is different from those carried-out on SGA treatments and this may impact multiple factors that might affect outcomes, including diagnostic modalities and study designs.

With respect to SGDAs, the most robust evidence is related to the use of RIS-LAI depot. RIS-LAI was found to be effective in preventing relapses of any mood symptoms (primary outcome) as well as for preventing manic symptoms compared to PBO, including BD patients with rapid cycling in whom RIS-LAI resulted more effective compared also to oral medications (Macfadden et al., 2009; Martinez-Aran et al., 2009; Kishi et al., 2016).

Furthermore, the use of RIS-LAI improved CGI-S (Savas et al., 2006; Yatham et al., 2007; Vieta et al., 2008; Macfadden et al., 2009; Vieta et al., 2012) and YMRS scores (Yatham et al., 2007; Macfadden et al., 2009; Quiroz et al., 2010), decreased number of hospitalisations and the length of stay (Vieta et al., 2008, 2012; Peuskens et al., 2010; Hsieh et al., 2017), and reduced discontinuation rates of current treatments (Vieta et al., 2008; Quiroz et al., 2010) and hetero-aggressive episodes (Vieta et al., 2008). When the study was observational and other drugs could be used along RIS-LAI, (Vieta et al., 2008), about one third of patients were receiving or introduced lithium, while all patients were on anticonvulsants or lithium throughout the study; this could have affected outcome, hence studies are needed to evaluate the ability of each treatment alone or combined in preventing a bipolar mood episode.

Although RIS-LAI did not show an efficacy in preventing depressive recurrences, at the same time this drug did not worsen depressive symptoms as did the FGDAs (Esparon et al., 1986; Macfadden et al., 2009; Hsieh et al., 2017).

The only study assessing the efficacy of Pal-P in SAD patients showed the efficacy of this drug in preventing psychotic, depressive, and manic symptoms both in add-on or monotherapy and in improving and maintaining functioning beyond symptom control (Fu et al., 2015). Further studies are needed to assess the efficacy of Pal-P in the maintenance treatment of BD, both in terms of manic and depressive relapses.

Similarly, the results of the study of Calabrese et al., (2017) investigating the efficacy of Ari-M in BD patients gave support to the FDA indication of this drug for the maintenance treatment of BD-I. In fact, in patients with BD-I who had a manic episode at study enrolment, Ari-M delayed the time to mood episode recurrence (primarily manic), without increasing depressive episodes.

Noteworthy, the predominantly antimanic vs. antidepressant preventive efficacy of LAIs in BD is consistent with their polarity index (Popovic et al., 2012) and with their use in patients with poor treatment adherence. In fact, several studies found that factors that have been related with poor adherence in BD and SAD include a rapid cycling course, a greater illness severity (Martinez-Aran et al., 2009; Perlis et al., 2010), the predominance of manic symptoms and a higher rate of recurrences and hospitalisations, but not depressive symptoms (Sylvia et al., 2014). In this sense, LAIs may represent an effective treatment strategy by increasing medication adherence and by reducing relapses in these subtypes of BD patients. To test the ability of LAIs medicines to supersede their oral counterparts in preventing mood episodes, study designs should focus on accurately assessing treatment adherence and clinical course in parallel groups receiving the same drug, one oral and the other LAI.

4.1. Limitations

The limitations of this review are the same of the studies it included, and include undisclosed inter site differences for the multisite trials, small sample sizes for the older LAI trials, inconsistent methodologies that prevented us from
performing a meta-analysis, and generally medium level of evidence. A comparison between LAIs and first generation depot neuroleptics is not feasible, since the older published studies lacked scientific rigour.

Summarizing, the level of evidence for the use of LAIs in the maintenance treatment of BD and SAD is still limited, since there are only a few large, controlled, randomised trials in the literature, but there are several clinical scenarios in which they may be a first-line option, with the exception of FGDAs, due to the risk of inducing depression. Examining the use of SGDAs, evidence reviewed on RIS-LAI suggests that this drug is effective as maintenance treatment in BD and SAD and in improving adherence to medication in these patients, through the efficacy on manic recurrences, without worsening depression. Similarly promising results have been found with Pal-P in SAD patients and with Ari-M in BD patients. Tentative indications for the use of LAIs in BD and SAD are shown in Table 2.

Further studies are needed on the use of LAIs in BD and SAD, especially assessing the newest drugs such as paliperidone and aripiprazole in special populations of BD patients, i.e. those with rapid cycling or with high numbers of manic relapses, in order to improve treatment adherence and the clinical course of BD. Moreover, the long-term impact of those compounds on cognitive and functional outcomes, which are heavily influenced by the number of manic recurrences (Sanchez-Moreno et al., 2018), should be addressed. Future studies should also focus on site of injection (deltoid vs. gluteal) (Heres et al., 2012) and timing of administration (twice vs. once-monthly vs. three-month), as well as on less invasive methods of drug level monitoring (Murr et al., 2017). 3-Month paliperidone has advantages and disadvantages over once-monthly injections, and so may prove to have aripiprazole lauroxil with its two-month option, although it has not as yet been tested in BD. We await studies with these novel LAI formulations to gain a complete picture of LAIs in the treatment of BD and SAD. Furthermore, the concomitant use of LAI antipsychotics and mood stabilizers should be adequately assessed like in Macfadden et al. (2009), as there is preliminary evidence

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that oral SGA antipsychotic add-on might protect against manic relapses/recurrences in BD.

Another issue needing clarification is whether side effects related to LAIs tend to be "long-acting" as their formulation. There always has been concern among clinicians as to this aspect, but reassuring data as to the similarity with the side effects observed with oral antipsychotics has been gathered over the years, with patients gradually adapting to these side effects (Knudsen et al., 1985; Marder, 1986). Although in one study LAIs compared favourably to their oral counterparts for what concerns side effects (Sağlam Aykut et al., 2017), there are still concerns regarding their dosing and availability (Taylor, 2009), as well as suicide risk (Gentile, 2013), that should be addressed by future studies.

In conclusion, we provide a take-home series of messages in Table 3, including each LAI’s specific actions and side effects that may limit their application in patients with bipolar or schizoaffective disorder.

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### Contributors

Drs. Pacchiarotti and Vieta conceived the review and provided indications for the design; Drs. Pacchiarotti and Kotzalidis designed the searches and conducted them, identified relevant literature and wrote the first drafts of the paper; Drs. Tiihonen, Verdolini, Murru, Goikolea, Valentí, and Aedo contributed in writing substantial portions of the manuscript; Prof. Vieta reviewed the final draft; all authors participated in Delphi rounds to reach consensus about study inclusion and approved the final version of the manuscript.

### Conflict of interest

Dr. Pacchiarotti has received CME-related honoraria, or consulting fees from ADAMED, Janssen-Cilag, and Lundbeck.

Dr. Tiihonen reported serving as a consultant to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Hoffman-La Roche, Janssen-Cilag, Lundbeck, Organon, and Finnish Medicines Agency; receiving fees for giving expert testimony to AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Otsuka, and Pfizer; receiving lecture fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Lundbeck, Novartis, Otsuka, and Pfizer; receiving grants from Stanley Foundation and Sigrid Jusélius Foundation; serving as a member of advisory boards for AstraZeneca, Eli Lilly, Janssen-Cilag, and Otsuka; and having research collaboration with Lilly and Janssen-Cilag.

Dr. Kotzalidis has no conflicts of interest.

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Dr. Goikolea has been a speaker or on the advisory board for Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly, Glaxo-Smith-Kline, Janssen-Cilag, Merck Sharpe and Dohme, Otsuka, Pfizer, Sanofi-Aventis.

Dr. Valentí has received grants from Eli Lilly & Co.; and has served as a speaker for Abbott, Bristol-Myers Squibb, GlaxoSmithKline, and Janssen-Cilag.

Dr. Aedo has no conflicts of interest.

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### Supplementary materials

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